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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,885	02/02/2004	Karl Y. Hostetler	UCSD1480-1	1066

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EXAMINER	
MAEWALL, SNIGDHA	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/770,885	HOSTETLER ET AL.	
	Examiner	Art Unit	
	Snigdha Maewall	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-12 and 14-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-12 and 14-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

1. Receipt of Applicant's Arguments/Remarks and amended claims, filed on 09/16/08 are acknowledged.

Claims 1, 22, 23, 24, 27, 39, 40, 41 and 42 have been amended. Claims 2-4, 13 and 59-61 have been cancelled. Accordingly, claims pending in this application are **1, 5-12 and 14-58.**

Claim Rejections - 35 USC § 112

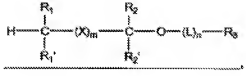
2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

3. Claims 1, 5-12 and 14-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

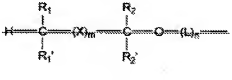
1. (Currently amended) A method for treating a pathological condition of ocular tissue, comprising contacting a therapeutically active complex with ocular tissue, wherein the complex has the structure I:



I

~~is formed by covalently attaching a moiety to a therapeutically active agent~~

wherein the pathological condition is selected from a the group consisting of macular degeneration, eye trauma, a pre-existing retinal detachment, ocular proliferative or vascular diseases, or diseases of elevated intraocular pressure or inflammation, ~~with the further proviso that the moiety is selected from a group consisting of sulfates, sulfonates, phosphates, lipids, phospholipids, carboxylates, sulfosuccinates, arginine esters, cholesterol esters, carbamates, carbonates, ketals, and the moiety having structure (I):~~



(I)

wherein in structure I:

each of R_1 and R_1' is independently selected from a the group consisting of –H, an optionally substituted –O(C_1-C_{24})alkyl, –O(C_1-C_{24})alkenyl, –O(C_1-C_{24})acyl, –S(C_1-C_{24})alkyl, –S(C_1-C_{24})alkenyl, and –S(C_1-C_{24})acyl, wherein at least one of R_1 and R_1' is not –H, and wherein the alkenyl or acyl optionally has between 1 and 6 double bonds,

each of R_2 and R_2' is independently selected from a the group consisting of –H, an optionally substituted –O(C_1-C_7)alkyl, –O(C_1-C_7)alkenyl, –S(C_1-C_7)alkyl, –S(C_1-C_7)alkenyl, –O(C_1-C_7)acyl, –S(C_1-C_7)acyl, –N(C_1-C_7)acyl, –NH(C_1-C_7)alkyl, –N((C_1-C_7)alkyl)$_2$, oxo, halogen, –NH_2, –OH, and –SH;

X is

L is selected from a the group consisting of a valence bond and a bifunctional linking group of the formula –J–(CR_2)$_t$–G–, wherein t is an integer having the value between 1 and 24, each of J and G is independently selected from a the group consisting of –O–, –S–, –C(O)O–,and –NH–, and R is selected from a the group consisting of –H, substituted or unsubstituted alkyl, and alkenyl;

R_3 is a phosphate or phosphonate derivative of a therapeutically active agent;

m is an integer having the value between 0 and 6; and

n is 0 or 1,

thereby treating the pathological condition.

Wherein R3 is a phosphate or phosphonate derivative of a therapeutically active agent is not seen to be disclosed in specification. Accordingly it is a new matter. Additionally no such structure of complex is also shown to be disclosed in the disclosure.

4. Claims 1, 5-12 and 14-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

5. Claims 1, 27 and 42 recite various substituents such as R1 R!', R2 and R2, g group and I group. Various substituents represent various chemical groups which are used for treating the pathological condition.'. The instant specification only provides few examples and recites only few specific compounds with specific substituents used to treat a pathological condition of an ocular tissue. Based on the instant disclosure, it obvious that the applicant was not in possession of all kinds of all and every possible combination of compounds in structure 1 attached to each and every therapeutic agent which one skilled in the art would be aware of. Additionally applicant claims treating a pathological condition of ocular tissue, comprising contacting a therapeutically active complex with ocular tissue. Recourse to the specification does not disclose forming therapeutic complex with any/each or every possible therapeutic agent. There are only few agents that are described which have been used in the invention. As such, by

providing broadest reasonable interpretation to the claim, claims as recited can be read on forming complex with any therapeutic agent particularly in the absence of specific recitation of specific agents which the applicant used at the time of invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of

species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus (therapeutic agents and several possible compounds with several different constituents claimed. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

The examiner suggests limiting the claims to compounds for which possession have been shown.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

6. Claim 1, 5-12 and 14-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

7. Claims 1, 22, 23, 27, 39, 40, 42, 59 and 60-61 recite the limitations having structure (I): wherein the various substituents vary to a large degree.

The specification discloses only certain compounds with specific substituents useful for treatment of pathological condition. In the absence of specific components and compounds as described under specific substituents and given the wide presence of various variables that exist in the chemical and pharmaceutical field, the disclosure as presented would entail one skilled in the art to undergo undue experimentation in order to make and use the invention.

Similarly in the absence of specific therapeutic agents, one skilled in the art would undergo undue experimentation to practice the claimed invention with each and every possible therapeutic agent in treating ocular condition. Claims 1, 27 and 42 as recited, read on any therapeutic agent forming complex with any lipid or any other moieties. However, the specification only discloses few examples and species.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988).

Due to the large quantity of experimentation necessary to determine the efficacy of complexed moiety in any species of therapeutic agent, the lack of direction/guidance

presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the breadth of the claims, which fail to recite any particular active agent and any specific compound undue experimentation would be required of the skilled artisan to make and/or use the claimed invention directed towards a method in treating a pathological condition of ocular tissue. The specification only teaches preparation of HDP-cCDV, HDP-P-GCV in treating pathological conditions claimed. Examiner suggests providing evidence in the form of technical experimental data to support the scope of enablement of each and every possible combination of complex in treating the claimed pathological conditions.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 5-12, 14-15 and 22-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (Feb. 2002) (herein onwards Cheng et al. I). (Investigative Ophthalmology & Visual Science, Feb. 2002, Vol. 43).

Cheng et al. disclose the intraocular drug delivery system using the free crystalline lipid prodrug of ganciclovir, HDP-P-GCV, as a prototype. Cheng et al. discloses a local

intravitreal drug administration for vitreoretinal diseases, which bypasses the blood-ocular barriers and allows higher intraocular drug levels and avoids many side effects associated with systemic therapy. The intraocular drug delivery may also provide constant and slow release drug. Cheng et al. further disclose that surgical placement and replacement of intravitreal implants can cause significant adverse effects, including vitreous hemorrhage, retinal detachment, and endophthalmitis. Cheng et al. disclose that the intravitreal injection of a long-acting drug preparation would be less invasive than surgery and thus in order to prove such, Cheng et al. have demonstrated in the article that crystalline HDP-P-GCV in the form of 8- to 43-micrometer particles may have utility in treating or preventing HSV retinitis when injected intravitreally as Infrequently as once a month or less frequently (see page 515, paragraph, 5 and column 2, first paragraph). The local retinal or lens toxicity observed with high doses may be eliminated, and antiviral duration could even be prolonged by using smaller drug particles, which may provide a better release rate and require less drug to maintain a therapeutic vitreous level with the advantage of a smaller drug depot (see page 521, 4th paragraph and column 2, first paragraph).

Because cheng's references teach that surgical placement and replacement of intravitreal implants can cause significant adverse effects, including vitreous hemorrhage, retinal detachment, and endophthalmitis. Cheng et al. disclose that the intravitreal injection of a long-acting drug preparation would be less invasive than surgery and thus in order to prove such, Cheng et al. have demonstrated in the article that crystalline HDP-P-GCV in the form of 8- to 43-micrometer particles have utility in

treating or preventing HSV retinitis when injected intravitreally as infrequently as once a month or less frequently (see page 515, paragraph, 5 and column 2, first paragraph). Retinitis can be characterized as one of the conditions of eye trauma, therefore Cheng's references renders the claimed limitations obvious.

Response to Arguments

10. Applicant's arguments filed 09/16/08 have been fully considered but they are not persuasive.

Applicant argues that retinitis is different from eye trauma and thus the prior art does not teach the claimed invention. Applicant's arguments are not persuasive because claim 1 does not only recite eye trauma, it also recites diseases of elevated inflammation which is related to retinitis. Applicants have not defined eye trauma anywhere in the specification, as such the prior art still renders the claimed invention obvious.

11. Claims 1, 5-12, 14-15 and 22-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (May 2000). (Investigative Ophthalmology & Visual Science, May 2000, Vol. 41, No. 6).

Cheng et al. disclose that Cytomegalovirus (CMV) infection of the retina is the most common infection in acquired immune deficiency syndrome (AIDS) patients. (See page 1523, first paragraph).
Ganciclovir (GCV) was the first drug to be approved for CMV infection in AIDS

patients. Ganciclovir is effective in treating CMV retinitis by intravenous administration, but the drug does not eliminate the virus from the retina, requiring long-term suppressive maintenance therapy. Systemic toxicity such as bone marrow suppression was also a problem. The sustained-release GCV implant is effective treatment for CMV retinitis and recurrent CMV retinitis, but complications from surgery such as endophthalmitis and retina detachment are sight threatening. Therefore, in an effort to overcome the disclosed threat, Cheng et al. developed a simple, in-office injectable local therapy that would be effective, minimally toxic, and long-lasting for treatment of CMV retinitis (page 1523, column 2, paragraph 2 and 3).

Cheng et al. further disclose the experimental treatment efficacy of 1-O-hexadecylpropanediol-3-phospho-ganciclovir (HDP-P-GCV (see figure 1 and section under pathologic evaluation of the retinisis, page 1524) and disclose that the antiviral agent, HDP-P-GCV, may be very useful as a local therapy for treating CMV retinitis, HSV retinitis, and other intraocular viral infections in both immunocompromised and immunocompetent individuals. This type of self-assembling liposomal prodrug provides a prototype for intraocular drug delivery and may be applied to the delivery of many currently available drugs for chorioretinal or vitreoretinal diseases (page, 1531, last paragraph).

Because Cheng's references discloses the experimental treatment efficacy of 1-O-hexadecylpropanediol-3-phospho-ganciclovir (HDP-P-GCV (see figure 1 and section under pathologic evaluation of the retinisis, page 1524) and disclose that the antiviral

agent, HDP-P-GCV, may be very useful as a local therapy for treating CMV retinitis, HSV retinitis, and other intraocular viral infections in both immunocompromised and immunocompetent individuals. Retinitis can be characterized as one of the conditions of eye trauma, therefore, Chengs references renders the claimed limitations obvious.

Response to Arguments

12. Applicant's arguments filed 09/16/08 have been fully considered but they are not persuasive.

Applicant argues that retinitis is different from eye trauma and thus the prior art does not teach the claimed invention. Applicant's arguments are not persuasive because claim 1 does not only recite eye trauma, it also recites diseases of elevated inflammation which is related to retinitis. Applicants have not defined eye trauma anywhere in the specification, as such the prior art still renders the claimed invention obvious.

13. Claims 16-21 and 53-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Cheng et al.) or (Cheng et al. I); (Investigative Ophthalmology & Visual Science, May 2000, Vol. 41, No. 6 and Feb. 2002, Vol. 43) as cited above in view of Unger (US Patent No. 6,120,751).

The teachings of Cheng et al. have been discussed above. Cheng et al. do not exclusively teach various nucleosides, antibody or AZT.

Unger discloses compositions comprising charged lipids, targeting ligands and the use of such compositions in drug delivery, targeted drug delivery, therapeutic imaging and

diagnostic imaging as well as their use as contrast agents (abstract). The composition comprises various nucleosides, antibody, polyclonal antibody, fab fragments and AZT (column 45 and 46, lines 67 and 1 and column 48, lines 18-25).

It would have been obvious to the one of ordinary skilled in the art at the time the invention was made to incorporate various therapeutic agents such as various nucleosides as cited above in the formulation of Cheng et al. since Cheng et al. suggest that assembling liposomal prodrug provides a prototype for intraocular drug delivery and may be applied to the delivery of many currently available drugs for chorioretinal or vitreoretinal diseases and Unger teaches that such a composition comprising nucleosides help in targeted delivery. A skilled artisan would have had a reasonable expectation of success in treating pathological condition of ocular tissue with a composition comprising therapeutic agents such as nucleosides.

Response to Arguments

14. Applicant's arguments filed 09/16/08 have been fully considered but they are not persuasive.

Applicant has not discussed this reference specifically, the rationale for combining the references have been discussed above. Applicants have specified several active ingredients, however, the claims as recited lack enablement for all kinds of active ingredient listed and the specification does not show possession of each and every active complex to treat pathological conditions claimed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S Kishore/

Primary Examiner, Art Unit 1612